02

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
PU9926-PCT		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/EP 00/ 06142	30/06/2000	30/06/1999
Applicant		
GYROS AB		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 2 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. 2

   [X] as suggested by the applicant.

   [ ] None of the figures.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 00/06142

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 F15C5/00 F16K13/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 F15C F16K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 643 247 A (J.M. FERNANDEZ ET AL.) 1 July 1997 (1997-07-01) column 4, line 66 -column 5, line 9 column 15, line 1 - line 48; figures 15A-15C	1
A	ICHIJO H ET AL: "Thermo-responsive gels" RADIATION PHYSICS AND CHEMISTRY,NL,ELSEVIER SCIENCE PUBLISHERS BV., AMSTERDAM, vol. 46, no. 2, 1 August 1995 (1995-08-01), pages 185-190, XP004051389 ISSN: 0969-806X cited in the application the whole document	1

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
1 November 2000	08/11/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Goetz, P

1

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 00/06142

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5643247 A	01-07-1997	AT 168497 T	15-08-1998
		AU 676023 B	27-02-1997
		AU 6231494 A	15-08-1994
		CA 2153990 A	04-08-1994
		DE 69411709 D	20-08-1998
		EP 0680659 A	08-11-1995
		JP 8510597 T	05-11-1996
		WO 9417538 A	04-08-1994

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
PU9926-PCT		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP00/06142	30/06/2000	30/06/1999
International Patent Classification (IPC) or national classification and IPC F15C5/00		
Applicant GYROS AB et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 4 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☒ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
22/01/2001	30.08.2001
Name and mailing address of the international preliminary examining authority:	Authorized officer

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP00/06142

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-17	as originally filed			
Claims, No.:				
5-10,16-23	as received on	25/05/2001	with letter of	23/05/2001
1-4,11-15	as received on	23/07/2001	with letter of	20/07/2001
Drawings, sheets:				
1/8-8/8	as originally filed			

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☐ contained in the international application in written form.
   - ☐ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1,13
Inventive step (IS)	Yes:	Claims	
	No:	Claims	2-12,14-23
Industrial applicability (IA)	Yes:	Claims	1-23
	No:	Claims	

2. Citations and explanations
   see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

   see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

Item V

Independent claim 1.

The document US-A-5 547 472 (D3) discloses in Figure 4 and column 3, line 57 to column 5, line 15:
a method of controlling flow of liquids in a micro channel structure comprising a micro channel (pores 12) and a chamber 7 in the microformat (column 4, lines 16-19), said method comprising the steps of:
providing in at least one position in said channel structure a plug of polymer material (stimulus responsive polymer) in said each position, said polymer material comprising an intelligent polymer having the property of responding to externally applied energy by changing its volume, said polymer material in a first state providing a first volume blocking said channel from liquid flow, and in a second state providing a second volume giving a free path-way for liquid flow; and
selectively applying energy of appropriate type and magnitude to the polymer material of said plug so as to cause the volume change between said two states, thereby bringing said polymer to a desired one of said first or second states.

Therefore the subject-matter of independent claim 1 does not meet the criterion of novelty (Articles 33(2) and 33(1) PCT).

Independent claim 13.

In the same way, D3 discloses in Figure 4 and column 3, line 57 to column 5, line 15:

a micro channel valve system, comprising a plurality of plugs of a polymer material comprising an intelligent polymer having the property of responding to externally applied energy by changing its volume, said plugs being provided at selected locations (pores) within at least one channel of a micro channel structure comprising the channel and a chamber in the microformat.

Therefore the subject-matter of independent claim 13 does not meet the criterion of novelty (Articles 33(2) and 33(1) PCT).

Dependent claims 2 to 12 and 14 to 23.

These dependent claims do not appear to contain any additional features which are not known nor obviously derivable from D3 or the prior art documents cited in the international search report.

Item VI

The publication: Micro Total Analysis System 2000, Ed. Van der Berg et al., Proceedings of the μTAS 2000 Symposium held at Enschede, The Netherlands 14-18 May, 2000, pages 45-48 and 147-150, by Liu et al and Madou et al, is a so-called P-document published prior to the international filing date of present application (30.06.2000) but later than the claimed priority date (30.06.1999). The present IPER is drawn on the assumption that the right to priority of present application is valid.

Item VII

In contradiction with the requirements of Rule 6.3 (b) (i) and (ii) PCT, the independent claims have not been cast in the two part form, with those features which in combination are part of the prior art (see document D3) being placed in the preamble.

The document D3 has not been identified in the description nor has the relevant background art disclosed therein been discussed. The requirements of Rule 5.1(a)(ii) PCT are, thus, not fulfilled.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
11 January 2001 (11.01.2001)

PCT

(10) International Publication Number
WO 01/02737 A1

(51) International Patent Classification[7]: F15C 5/00, F16K 13/10

(21) International Application Number: PCT/EP00/06142

(22) International Filing Date: 30 June 2000 (30.06.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
9902474-7 30 June 1999 (30.06.1999) SE

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(74) Agents: ROLLINS, Anthony, John et al.; Nycomed Amersham plc, Amersham Laboratories, White Lion Road, Amersham, Buckinghamshire HP7 9LL (GB).

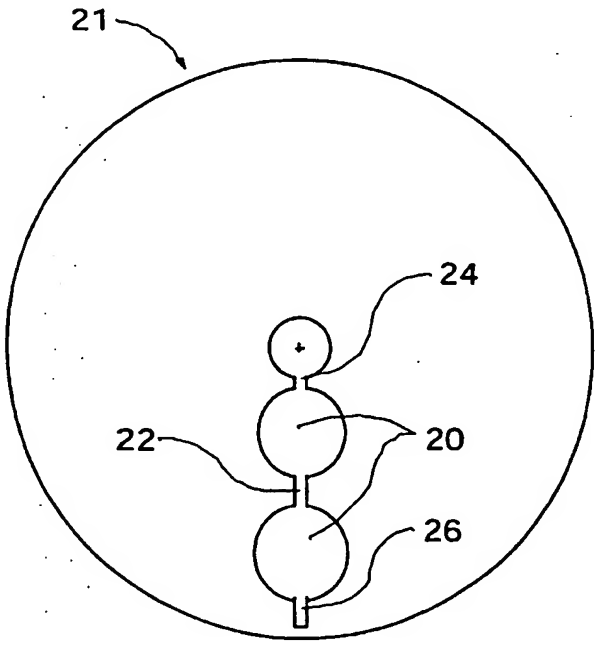
(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *With international search report.*
— *Before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments.*

[Continued on next page]

(54) Title: POLYMER VALVES



(57) Abstract: The invention relates to a method of controlling flow of liquids in a micro channel structure. It comprises providing in said micro channel structure plugs (34) of polymer material in said structure, said polymer material in a first state blocking said channel from liquid flow, and in a second state providing a free path-way (32) for liquid flow. Energy is selectively applied so as to cause said polymer to enter a desired one of said first or second states. It also relates to a micro channel valve system, comprising a plurality of such plugs (34). Additionally it comprises a chemical reactor, comprising a plurality of micro chambers interconnected by micro channels, having a valve system according to the invention.

WO 01/02737 A1

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

POLYMER VALVES

The present invention relates to devices and methods for controlling liquid flow in micro channel structures.

Background of the Invention

In recent years micro chamber and channel structures for performing various reactions and analyses have gained wider use. Examples of scientific fields employing devices comprising such micro channel structures are separation techniques (gas chromatography, electrophoresis), cell biology, DNA sequencing, sample preparation, combinatorial chemistry just to mention a few.
The terms "chamber" and "cavity" will in the context of the invention be used interchangeable if not otherwise specified. A chamber or cavity may be a part of a microchannel.

In certain applications it is common to provide a plurality of micro chambers in which reactions are performed, or in which material is incubated for later use etc. It may often be desirable to move the material from one chamber to another. To this end the chambers are connected by micro channels. Obviously it may become necessary to provide some means of closing said channels after the material has passed therethrough, and also it might be desirable to have the possibility to reopen the channel in order to enable more material to pass through.

In WO 94/29400 there is disclosed a microfabricated channel system. This system is designed for i.a. chemical analytical use, such as electrophoresis and chromatography. In one type of structure a channel and/or cavity system is defined between two plane material layers, the recesses which correspond to the channels and cavities, respectively, being formed in one or both of the opposed layer surfaces. The layers are usually bonded together by gluing.

Alternatively they may be fused together if the two layers consist of thermoplastic material.

In WO 9721090 there is disclosed a microfluidic system having a valve function based on the property of a polymer. Opening of the valve function is actuated by external application of heat. However, the valve function has the drawback that disrupting the heating, e.g. by cooling, will not close the valve.

The type of systems concerned in the present invention may have channels that are of capillary dimensions for liquid flow/transport. The distance between two opposite walls in a channel may be ≤ 1000 μm, such as ≤ 100 μm, or even ≤ 10 μm, such as ≤ 1 μm. This type of systems may also contain one or more distinct chambers connected to the channels and having volumes being ≤ 500 μl, such as ≤ 100 μl and even ≤10 μl such as 1 μl. The depths of the chambers may typically be in the interval ≤ 1000 μm such as ≤ 100 μm such as ≤ 10 μm or even ≤ 1 μm.

The lower limit for the dimensions is set by manufacturing technology limitations, but can be of the nanometer scale, such as > 10 nm, > 100 nm or > 1000 nm.
One or more liquid transportation systems of this type may be placed on a common plate, for instance rotatable, such as a disc of CD-type. In case of rotatable forms the liquid may be forced through one or more segments of the transportation system by rotating the disc (centripetal force), i.e. the liquid is transported in an outward direction relative the center of the disc. Other types of pressure generating systems may also be used.

A device having one or more liquid transportation system comprising channels and chambers with a depth ≤ 1000 μm, such as ≤ 100 μm or even grounder than 10 μm such as ≤ 1 μm, are further on called a microfabricated device or a micro chamber and channel structure/system or a microfluidic structure/system. The

chambers/channels and also the device, structure and system are said to be in the microformat. A microfabricated device typically has its channels and chambers in one plane, such as in the surface of a plate, for instance on a disc. The plate may be circular, oval, rectangular (including in form of a square) or of any other 2D geometric form.

The channels and/or chambers define a flow path pattern in the system, which is delineated by barriers. The barriers can be in form of physical walls, bottoms and tops that are located on or in a planar surface. Hydrophobic barriers combined with aqueous liquids and vice versa for non-polar liquids (see WO 99/58245) have been suggested for defining flow paths and for directing the liquid flow, i.e. to replace the walls and the like in microfabricated devices. There is typically also a second surface applied against the pattern and acting as a top covering the pattern and preventing evaporation of liquid (except for minor parts/dots intended for addition/removal of liquids).

Liquid transportation systems of he type referred to above may also contain valves, pumps, filters and the like.

As mentioned above, in a particular application, a chamber and channel structure is provided in or on a plastic disk. Two or more micro chambers in sequence are aligned radially via a channel. When the disk is spun, material in a chamber located near the center will migrate through the channel to an outwardly located chamber, thereby providing a controllable flow path for reagents to pass from one chamber to another.

However, it is of course difficult to control the flow. The spinning of the disk could be correlated with some position indicating means for locating a sample at a certain point in time, but absent a valve function, there will always be some "spill over" between chambers.

It is known to employ so called stimulus-responsive materials for a number of purposes, e.g. in micro-machines, separation, drug delivery systems etc. This type of material and preparation thereof is discussed in *Radiat. Phys. Chem.* Vol. 46, No 2, pp185-190,1995, in an article entitled "Thermo-responsive gels", by Ichijo et al.

One possible use is an automatic gel valve provided in a tube. A net is attached to cover the outlet of the tube and a porous PVME (poly(vinyl methyl ether)) gel plug is inserted into the tube and positioned on the net. In response to hot water flowing out through the tube, the gel collapses and the hot water was allowed to freely pass through. When cold water is introduced, the gel reversibly regains its swollen state, thereby blocking the outlet. This concept for a valve function is not possible to apply in a multi-valve structure, since only one gel plug can be inserted in a tube in this way. The already introduced plug will hinder the insertion of subsequent plugs downstream. It is also impossible to arrange subsequent plugs upstream of the already positioned plug, since it will be impossible to provide the obstructing net structure for the upstream located plugs.

In US-5,547,472 (Onishi et al) a perforated balloon attached to a catheter was coated with a stimulus-responsive polymer, enabling the pores to be closed or opened in response to e.g. temperature changes. The polymer is bonded to the surface of the balloon and does not appear to be introduced into the pores.

During the priority year, approaches within the same field as the invention have been published by Beebe et al (Nature 404 (April 6, 2000) 588-590), and Liu et al and Madou et al (in Micro Total Analysis System 2000, Ed. Van der Berg et al., Proceedings of the μTAS 2000 Symposium held at Enschede, the Netherlands 14-18 May, 2000, pages 45-48 and 147-150, respectively) .

Summary of the Invention

Thus, there is a need for means and methods of controlling the liquid flow in micro channel structures, which do not suffer from the problems discussed above. In particular it is desirable and an object of the invention to provide a plurality of selectively operable valve functions arranged one after the other in one capillary channel, optionally between reaction chambers in a micro channel structure.

This object is achieved with the method as claimed in claim 1, and the micro channel valve system as claimed in claim 13, and the chemical reactor as claimed in claim 19, respectively.

Thereby an intelligent polymer (= stimulus-responsive polymer) is employed, having the capability of responding to externally applied energy (stimulus), by changing a property of the polymer so as to change its volume, thereby occupying more or less of the space in which the polymer is confined. For intelligent polymers the change is reversible meaning that once a stimulus (energy) applied is removed then the polymer returns back to its starting volume. By applying energy of appropriate type and magnitude it will be possible to cause a volume change in a desired direction (increase or decrease) to either open or close a pathway through a valve comprising this kind of polymer in a microchannel. It follows that the term "applying energy" includes both positive and negative energy values, i.e. removal and supplying energy.

The required type of energy depends, among others, on the polymer, and includes the so called free energy of chemical systems. The application of energy may take place by heating, irradiation (UV, IR etc) etc or by changing the chemical composition of the liquid in contact with the polymer (e.g. change of pH, of solvent, of concentrations of compounds reacting reversible with the polymer etc). By the term "externally applied" is meant external to the polymer, i.e. application of energy has to take place either via the

walls surrounding the polymer or via the liquid in contact with the polymer. This also includes applying the energy to a liquid present in a channel for transport therein by the liquid to the stimulus-responsive polymer in the inventive valve.

In a preferred embodiment the polymer responds to externally applied heat or to external cooling by undergoing a conformational change.

In another embodiment the polymer responds to an applied electrical field.

In still another embodiment the polymer responds to light.

The polymer may in a further embodiment respond to magnetic fields.

Preferably the polymer is provided in gel form (solvated form, closed valve), disposed inside a channel and retained in a fixed position, or even anchored to at least one surface of said channel. When activated, the polymer contracts (the gel collapses or desolvates, opened valve) leaving a free pathway in the channel along that surface or those surfaces to which the polymer is not anchored.

Brief Description of the Drawings

The invention will now be described with reference to non-limiting examples and with reference to the attached drawings, in which

Fig. 1 shows an example of a micro channel and chamber structure according to WO 94/29400, wherein the invention may be employed;

Fig. 2 shows a top view of the structure of Fig. 1 in case the microstructure comprises channels and chambers;

Fig. 3a is a cross section through a channel of a micro channel structure wherein a plug of a stimuli responsive gel is located in a channel, without being anchored to any surface, and in a swollen state;

Fig. 3b is the same cross section as in Fig. 3a, where the polymer has been stimulated to collapse, thereby providing a free flow path;

Fig. 3c is a cross section through a channel of a micro channel structure wherein a plug of a stimuli responsive gel is anchored in one surface of the channel, and in a swollen state;

Fig. 3d is the same cross section as in Fig. 3a, where the polymer has been stimulated to collapse, thereby providing a free flow path;

Fig. 3e shows a cross section of a channel in which the polymer has been anchored to three surfaces of a channel, and is in a contracted state;

Fig. 4a is a perspective view, partially in cross section of a channel having a grid as a mechanical means to prevent a gel plug from moving;

Fig. 4b is a perspective view, partially in cross section, of a channel having a plurality of pointed protrusions provided over a surface of a channel, providing anchoring means to prevent a gel plug from moving;

Fig. 4c is a perspective view, partially in cross section of a channel having side rooms in which a gel plug can be inserted, to prevent it from moving;

Fig. 5a is microphotograph of the gel prepared in Example 1 in a swollen state; and

Fig. 5b is the same gel as shown in Fig. 5a in contracted state.

Detailed Description of Preferred Embodiments of the Invention

For the purposes of this application, the term "chemical reactor" shall be taken to mean any structure capable of housing chemical and/or biological reagents or reaction partners, and in which these agents can react, i.e. interact with each other, for the purposes of synthesis, analysis, separation or other chemical, physical-chemical or biological processes.

In Fig. 1 there is shown a cross section of a microfabricated channel structure, which forms the subject matter of WO 94/29400.

The structure in Fig. 1 comprises two elements 11, 12 having opposed plane surfaces bonded together. One or both of the surfaces have open channels 14 and or cavities provided therein. The bonding may be effected by applying a thin layer 13 of a solution of a material capable of fusing with and having a lower melting point than that of the materials of the two element surfaces, in a solvent which substantially does not dissolve the element surface material or materials. Solvent is removed, the element surface are brought together and heated to melt the layer 3 so as to bond the surfaces together.

In Fig. 2 a top view of a simplified, exemplary CD (compact disk) type of device 21 is shown, having a chamber and channel structure that may be made e.g. in accordance with the disclosure of WO 94/29400.

Thus, the disk comprises two chambers 20 connected via a channel 22. There is also provided an inlet channel 24 having an upward opening (not shown) for the introduction of reagents, and an outlet channel 26, having an opening (not shown) for the discharge of reacted material.

This particular configuration could be used for e.g. performing a sequential reaction in two steps, one in each chamber 20, the first step being carried out in the innermost (with respect to the radial direction) chamber, and the second in the outermost chamber. This structure thus constitutes a "chemical reactor" as defined above, e.g. for carrying out a synthetic reaction. However, in order to be able to do this in a controlled way, a valve function according to the invention is provided in at least the connecting channel 22 and the outlet channel 26. Thereby the second chamber can be isolated from the first, and the reaction in the first chamber can be carried out to the desired extent. Thereafter the valve is activated and the reaction mixture in the first chamber can be transported into the second chamber where new reagents may be present and the second step is carried out.

The driving force for the transport of material between the chamber can be a centrifugal field created by spinning the disk. For electrophoresis applications, an electric field would be employed. If a column like configuration is employed, i.e. the chambers are arranged vertically, the first above the second, gravity could be used as driving force for the transport.

Now the valve function according to the invention will be described in detail with reference to Figs 3a-3e.

According to a first embodiment of the invention (Figs. 3a and 3b), a polymer 34 capable of effecting a structural change in response to a stimulus (stimulus responsive polymer), is placed in a channel 32 in a channel and chamber micro structure of the type described

above. When exposed to said stimulus, the polymer will collapse or contract, and leave at least a fraction of the channel in which it is situated free for liquid to flow there through

According to another embodiment of the invention, a polymer capable of effecting a structural change in response to a stimulus, is anchored in a channel 32 in a channel and chamber micro structure of the type described above. The polymer is anchored in such a way that when stimulated to collapse or contract, it has the possibility to leave at least a fraction of the channel in which it is situated free for liquid to flow through. Normally the cross section of the channels will be rectangular (see Fig. 3c), that is there will be four walls 31a-d, essentially perpendicular to each other. For a configuration of this type, the polymer 34 would preferably be anchored (schematically indicated at 36) to one, two or even three of the walls in said channel. This is shown schematically in Fig. 3c, where the polymer is shown to be in its swollen state, thereby blocking the channel completely. In fig. 3d a situation is shown where the polymer has been stimulated, e.g. by heating, such that it collapses, thereby opening the channel 32 to liquid flow. Finally, in Fig. 3e an embodiment is shown where the polymer gel 34 has been anchored in three walls of a channel. When stimulated by e.g. heat, the polymer strives to contract, but since it is attached to the walls on three sides, it will form a concave upper surface, leaving a free pathway 32 for fluid flow.

There are two main alternatives for bonding the stimulus-responsive polymer to the channel wall:

(a) chemical bonding/anchoring including covalent attachment or physical adsorption (for instance via ionic forces, van der Waals forces, dipole-dipole interactions etc, and

(b) retainment by mechanical means, for instance in chambers with narrow outlets and/or inlets (obstructions).

Alternative (a) requires that the polymer material is only partially bonded to the channel surface, i.e. there should be a non-bonded

part leaving a free fluid pathway between the polymer material and the channel surface when the polymer material is in a contracted state. Thus, this variant requires that bonding is occurring only on a fraction of the contact area between the microchannel surface and the plug in a swelled state.

The stimulus-responsive polymer may be bonded to the channel wall e.g. by effecting cross-linking reaction between polymer units of the wall material and the stimulus-responsive polymer respectively (= covalent anchoring/attachment/bonding). There are many ways of anchoring the polymer available to the skilled man, a couple of which are given as non-limiting examples below.

1) For polymers prepared by radical polymerization (e.g. polyacrylamides, polyacrylates, polymethacrylates or polyvinylamides) the channel surface can be modified to contain reactive groups capable of participating in the polymerization. Such groups can be active as initiators (e.g. azo or peroxide groups), copolymerizable groups (e.g. double bonds) or chain transfer groups (e.g. thiols or tertiary amines). Examples of ways to introduce the reactive groups are listed below:

- reacting glass, silica or silicon surfaces with a methacryl silane, a vinyl silane or a thiol silane.
- coating various surfaces with a thin layer of a polymer containing double bonds, such as allyl glycidyl agarose, polybutadiene or an unsaturated polyester resin.
- subjecting the polymer surfaces to plasma (glow discharge) treatment under such conditions that double bonds are formed on the surface.

2) More generally applicable ways could be to provide a rough surface with possibilities for mechanical interlocking of the polymer or to create an interpenetrating polymer network in the interphase between the polymer and a polymeric substrate.

It is also possible to use mechanical means to retain the polymer gel in a fixed position. These options will be described further in the Examples below.

The material in said micro channel surface can be subjected to a variety of surface treatments, such as wet etching, plasma treatment, corona treatment, UV treatment, grafting, adsorption coating, in order to improve the surface properties.

The stimulus, which can cause a structural change of the polymer in the pores, is selected from pH, ion, solvent composition, chemical substance, heat, electricity and light such as ultraviolet radiation. The structural change of polymer is swelling and contraction. The invention utilizes the nature of intelligent polymers that an external stimulus can trigger a reversible structural change between a solvated state and a desolvated state.

An important feature of the polymers used in the valves of the present invention is that they switch from a swelled state (solvated state) to contracted state (desolvated state) or vice versa in a reversible manner as discussed elsewhere herein. Thus the state at hand is dependent on the level/intensity of a stimulus applied, meaning for instance that above a certain critical level/intensity (magnitude) of the stimulus one state is at hand. For chemical substances the level/intensity typically corresponds to concentrations. When going below the critical level, the polymer is transformed to the other state. For a thermo-responsive polymer having a lower critical solution temperature (LCST), an increase in temperature passing the LCST will cause a switch from the solvated to the desolvated state and vice versa when changing the temperature in the opposite direction. When using a polymer having an upper critical solution temperature (UCST) the temperature increase will result in a switch from a desolvated state to a solvated state.

For example, a polymeric electrolyte gel is known to undergo a structural change owing to an osmotic pressure change by electrolyte ions in the polymer chain and interaction of electrolyte ions with a solvent. Then the polymeric electrolyte gel undergoes reversible contraction in response to a change of pH, solvent composition and ion concentration. An electric stimulus (in terms of potential, voltage and current) can be effectively utilized for the polymers contraction response since it can bring a local change of pH or ion concentration. Among non-ionic polymers, e.g. polymers and copolymers of vinyl methyl ether and N-isopropylacrylamide undergo a change between hydrophilic and hydrophobic states in response to heat and provide a contraction response in an aqueous solvent. Then by utilizing heat generation by electric resistance or heat of mixing, the effective diameter of the pores can be changed. A stimulus given by a chemical substance is such that polymer chains swollen in pores are contracted if a complex is formed by utilizing hydrogen bonds or the like. For example, if a carboxylic polymer swollen in pores is contacted with an agent containing a polyether, the polycarboxylic acid reacts with the polyether to form a high molecular weight complex with concomitant contraction, resulting in the pores increasing an open passage for fluids. The valves according to the invention are provided at selected points in a micro channel system. They can be prepared e.g. by photopolymerizing the stimulus responsive polymer in situ, where the irradiation is made through a mask, such that the polymer is only formed in the illuminated areas. After e.g. heat contraction of the polymer, residual monomers can be washed out of the channel system. It is also conceivable as an alternative to irradiation with light to employ microwaves, electron beams or any other type of radiation that is possible to mask off.

A further conceivable method is to form the polymer in the entire channel system, and then selectively degrading it (e.g. by light or radiation) everywhere except in the designated areas. The

degradation products would then be washed out after contraction of the valve areas.

The invention will now be illustrated by way of the following non-limiting examples.

EXAMPLES

In the following Examples a CD (compact disk) type device comprising micro channels and chambers as shown schematically in Fig. 2 can be used.

Example 1

N-isopropylacrylamide (0.5 g) and N,N-methylene bisacrylamide (0.01 g) was dissolved in water (4.0 ml). 0,1 ml of a photo-initiator (Irgacure 184, Ciba-Geigy, 100 mM in ethylene glycol) was then diluted in 0.5 ml water, before mixing it with the monomer solution. A drop of the monomer solution was transferred to a channel in a microfabricated CD disc made of plastic (polycarbonate), and covered by a microscope glass cover slip. The monomer solution inside the channel was then illuminated with UV light through the glass cover slip for 10 minutes in order to polymerize the monomers .

When the polymerization was completed, a hydrostatic pressure using an aqueous dye solution was applied to the inlet of the channel. No liquid was seen to flow through the channel (see Fig. 5a). The CD disc was then left at 40°C for 5 minutes, and a hydrostatic pressure was again applied to the channel. This time the liquid immediately flowed through the channel (see Fig. 5b). The CD disc was then allowed to return to room temperature, and again a hydrostatic pressure was applied. No liquid flowed through the channel. A picture of the valve before and after heat treatment is shown in Fig. 5a and 5b respectively.

Example 2

A microscope cover glass was wiped with methacryloxytriethoxysilane and rinsed with water and ethanol. A gel-forming solution was prepared from 0.5 g N,N-diethylacrylamide, 10 mg N,N'-methylenebisacrylamide, 6.5 ml distilled water and 0.1 ml of a 0.1 M solution of Irgacure-184 in ethylene glycol. A droplet of this solution was placed in a channel of a polycarbonate CD disc having a recessed 100 µm deep channel pattern on its surface, and a microscope cover glass was placed over the droplet with the treated side facing downwards. The package was placed on a cold steel plate under an array of low pressure mercury lamps and illuminated for 5 min to polymerize the monomers. A transparent gel was formed in the channels, which turned opaque upon heating to 45°C, and again turned transparent when it was cooled below room temperature. An aqueous dye solution was able to penetrate the channel system at 45°C, thus proving that a free path-way for fluid flow was provided. At room temperature the channel was blocked and no dye solution penetrated. The cover glass was then pryed.

Example 3

A gel-forming solution was prepared from 0,5 g N,N-diethylacrylamide, 10 mg N,N'-methylenebisacrylamide, 6,5 ml distilled water and 0,1 ml of a o,1 M solution of Irgacure-184 in ethylene glycol. A droplet of this solution was placed in a channel of a polycarbonate CD disc having a recessed 100 µm deep channel pattern on its surface, and a microscope cover glass was placed over the droplet. The package was placed on a cold steel plate under an array of low pressure mercury lamps and illuminated for 5 min to polymerize the monomers. A transparent gel was formed in the channels, which turned opaque upon heating to 45°C, and again turned transparent when it was cooled below room temperature. An aqueous dye solution was able to penetrate the channel system at 45°C, thus

proving that a free path-way for fluid flow was provided. At room temperature the channel was blocked and no dye solution penetrated.

Example 4

The same procedure as in Example 2 was repeated, but the cover glass was partially masked with an aluminum mask during illumination. The thermo-responsive gel was formed only in the illuminated parts of the channel system.

Example 5

A micro channel structure in a microfabricated CD disc 40 made of plastic (polycarbonate) is made, having the structure as shown schematically in perspective in Fig. 4. In this case there are provided mechanical obstructions in the channel 44 at the points where the valve is desired. These obstructions can be in the form of a grid of vertically arranged pins 42, as shown in Fig. 4a which is a cross section through a substrate in which a channel having such obstructions has been made. The gel (not shown) is polymerized in the channel upstream of the grid, using the same procedure as in Example 1.

When the polymerization is completed, a hydrostatic pressure using an aqueous dye solution is applied at room temperature to the inlet of the channel. No liquid was seen to flow through the channel. The CD disc is then left at 40°C for 5 minutes, and a hydrostatic pressure is again applied to the channel. This time the liquid immediately flowed through the channel. The CD disc is then allowed to return to room temperature, and again a hydrostatic pressure is applied. No liquid flowed through the channel.

Example 6

A micro channel structure in a microfabricated CD disc made of plastic (polycarbonate) is made, having the structure as shown schematically in Fig. 4b. In this case there are provided mechanical obstructions in the form of protrusions 46 in the channel, distributed over the area where the polymer plug is to be located, i.e. at the point where the valve is desired. These obstructions can be shaped in the same way as those shown in Fig. 4a, or could be shorter, rather like nipples, as shown in Fig. 4b, and will act as retaining elements for the gel. The gel is polymerized (not shown) in the channel in the area where the pins are located, using the same procedure as in Example 1. Thus, the pins will be molded inside the gel plug, thereby preventing it from moving in the channel.

When the polymerization is completed, a hydrostatic pressure using an aqueous dye solution is applied at room temperature to the inlet of the channel. No liquid is seen to flow through the channel. The CD disc is then left at 40°C for 5 minutes, and a hydrostatic pressure is again applied to the channel. This time the liquid immediately flowed through the channel. The CD disc is then allowed to return to room temperature, and again a hydrostatic pressure is applied. No liquid flowed through the channel.

Example 7

Of course other anchoring methods may be employed. One alternative is to provide a widened portion of the channel, such as the "side rooms" 48 as shown schematically in fig. 4c. A gel plug is provided such that it is "anchored" in the side rooms of the channel 44. If the side rooms are made large enough, the plug will be effectively prevented from moving in the channel under hydrostatic pressure.

CLAIMS

1. A method of controlling flow of liquids in a micro channel structure comprising a micro channel, said method comprising the steps of:

providing in at least one position, and preferably in a plurality of positions in said micro channel structure a plug of polymer material in each said position, said polymer material having the property of responding to externally applied energy by changing its volume, said polymer material in a first state providing a first volume blocking said channel from liquid flow, and in a second state providing a second volume giving a free path-way for liquid flow; and

selectively applying energy of appropriate type and magnitude to the polymer material of a selected one of said at least one plug so as to cause the volume change between said two states, thereby bringing said polymer to a desired one of said first or second states.

2. The method of claim 1, wherein said polymer material is selected from the group of polymers consisting of heat responsive polymers, light responsive polymers, magnetically responsive polymers, pH responsive polymers and polymers responsive to electric fields.

3. The method of anyone of claims 1-2, comprising that the said polymer material at least partially is anchored to a surface inside said micro channel.

4. The method of anyone of claims 1-3, wherein the polymer material is chemically bonded to the material in said micro channel surface.

5. The method of anyone of claims 1-3, wherein the polymer is anchored in the micro channel by means of a mechanical obstruction in the microchannel.

6. The method of any preceding claim, wherein the material in said micro channel surface comprises a material selected from plastics, e.g. polycarbonates, polystyrenes, cycloolefin polymers; rubbers; metals; carbon; inorganic oxides, nitirides, carbides; silicon; quartz.

7. The method of any preceding claim, wherein the material in said micro channel surface has been subjected to a surface treatment, such as wet etching, plasma treatment, corona treatment, UV treatment, grafting, adsorption coating.

8. The method of any preceding claim, wherein the step of applying energy comprises heating the polymer material and the polymer material comprises a heat responsive polymer.

9. The method of claim 8, wherein said heating is performed by irradiating with electromagnetic radiation, e.g. light, microwaves or infra red radiation, and the polymer material comprises a polymer responsive to electromagnetic radiation, e.g. light, microwaves or infra red radiation).

10. The method of any of claims 1-7, wherein the polymer is light sensitive and the step of applying energy comprises illuminating the polymer material with light of a suitable wave length, and the polymer material comprises a light responsive polymer.

11. The method of any of claims 1-7, wherein the step of applying energy comprises exposing the polymer material to a

magnetic field, and the polymer material comprises a magnetic responsive polymer..

12. The method of any of claims 1-7, wherein the step of applying energy comprises exposing the polymer material to an electric field, and the polymer material comprises a polymer responsive to electricity.

13. A micro channel valve system, comprising

a plurality of plugs (34) of a polymer material having the property of responding to externally applied energy by changing its volume, said plugs being provided at selected locations within at least one channel (31a-d) of a micro channel structure (20, 22, 24, 26).

14. The valve system according to claim 13, wherein said polymer material is selected from the group of polymers consisting of heat responsive polymers, light responsive polymers, magnetically responsive polymers, polymers responsive to electric fields.

15. The valve system according to anyone of claims 13-14, said polymer material comprising a polymer being selected from the group of polymers consisting of polyvinylethers, polyacrylamides, polyvinylamides, polyalkyleneglycols, celluloseethers, polyacrylates, polymethacrylates; and polymers of N,N-diethylacrylamide, N,N-diethylbisacrylamide, N-vinylcaprolactam, and a polymer obtained by the polymerization of N-isopropylacrylamide and N,N-methylene bisacrylamide.

16. The valve system according to any of claims 13-15, wherein said polymer material is anchored inside said micro channel by chemical bonding.

17. The valve system according to any of claims 13-16, wherein said polymer plug is anchored only over a fraction of the contact surface between the plug in a swelled state and the inner surface of said micro channel (partial anchoring).

18. The valve system according to any of claims 13-16, wherein said polymer plug is retained in a fixed position inside said micro channel by mechanical means.

19. A chemical reactor, comprising a plurality of micro chambers (20) interconnected by micro channels 22, 24, 26), having a valve system according to any of claims 13-18, provided in at least one of said micro channels.

20. The chemical reactor as claimed in claim 19, wherein said chambers and channels are provided in a planar substrate (21).

21. The chemical reactor as claimed in 20, wherein the substrate is of a material selected from the group consisting of plastics e.g. polycarbonates, polystyrenes, cycloolefin polymers; rubbers; metals; carbon; inorganic oxides, nitirides, carbides; silicon; quartz.

22. The chemical reactor as claimed in any of claims 20-21, wherein the substrate is circular.

23. The chemical reactor as claimed in any of claims 20-21, wherein the substrate is rectangular.

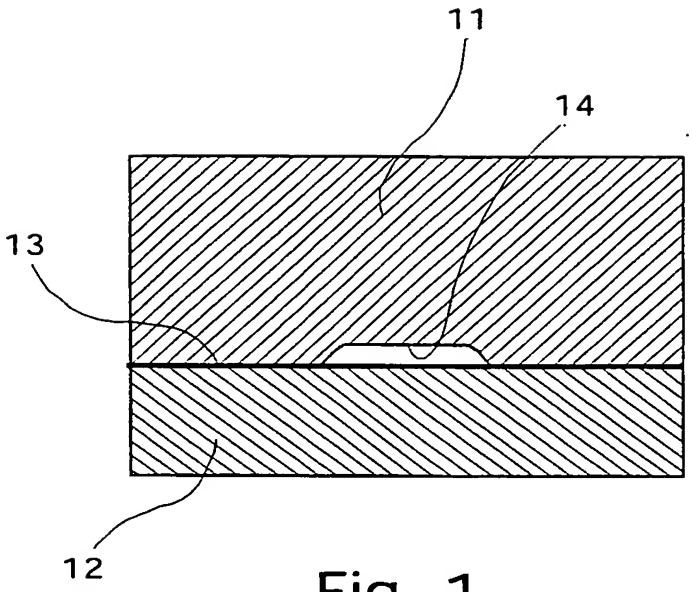


Fig. 1

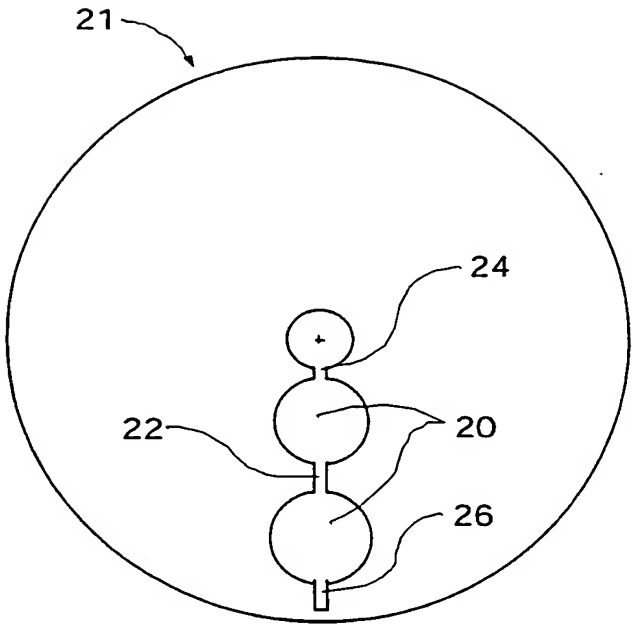


Fig. 2

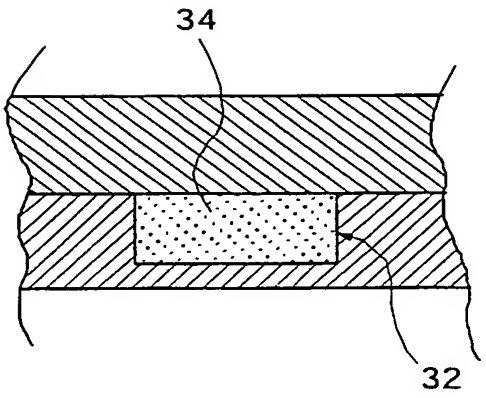


Fig. 3a

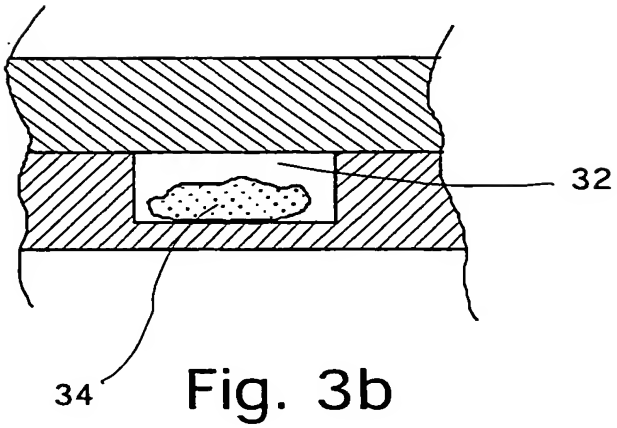


Fig. 3b

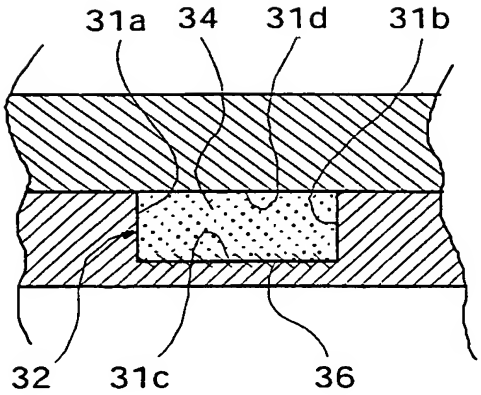


Fig. 3c

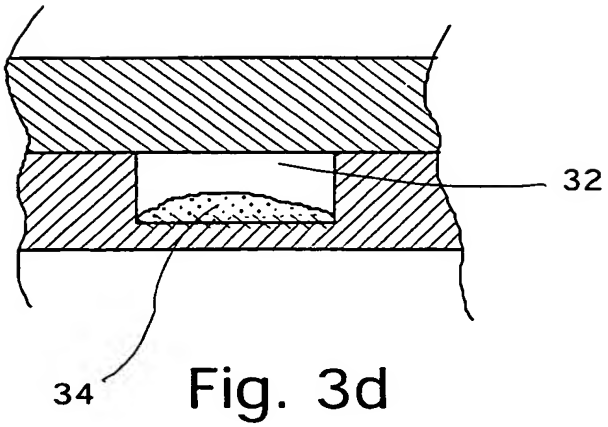


Fig. 3d

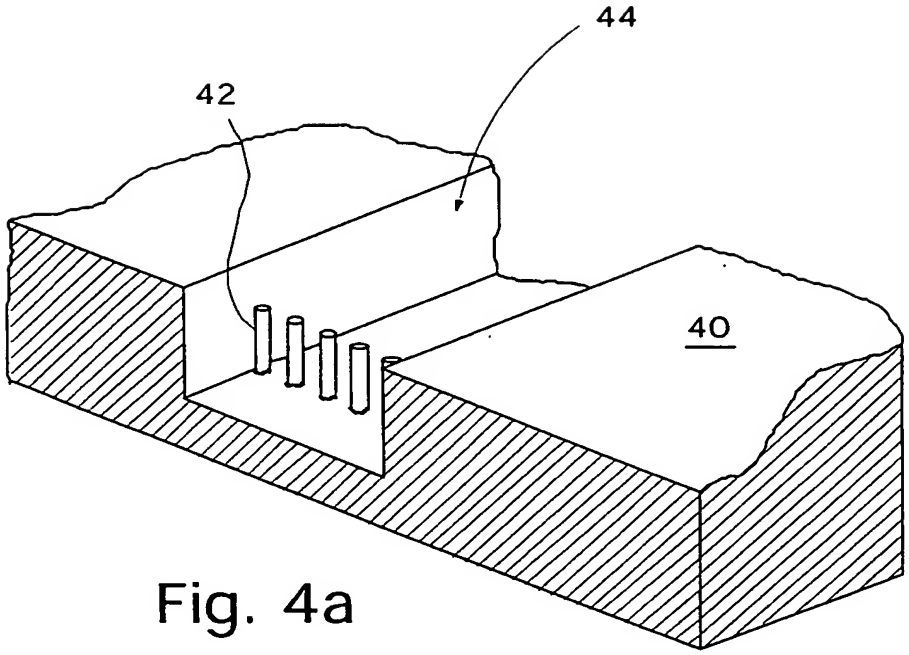


Fig. 4a

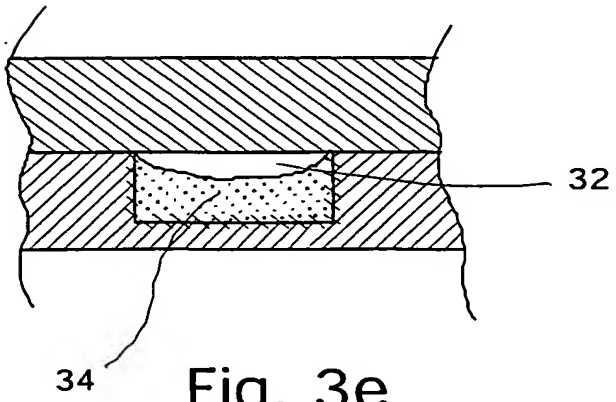


Fig. 3e

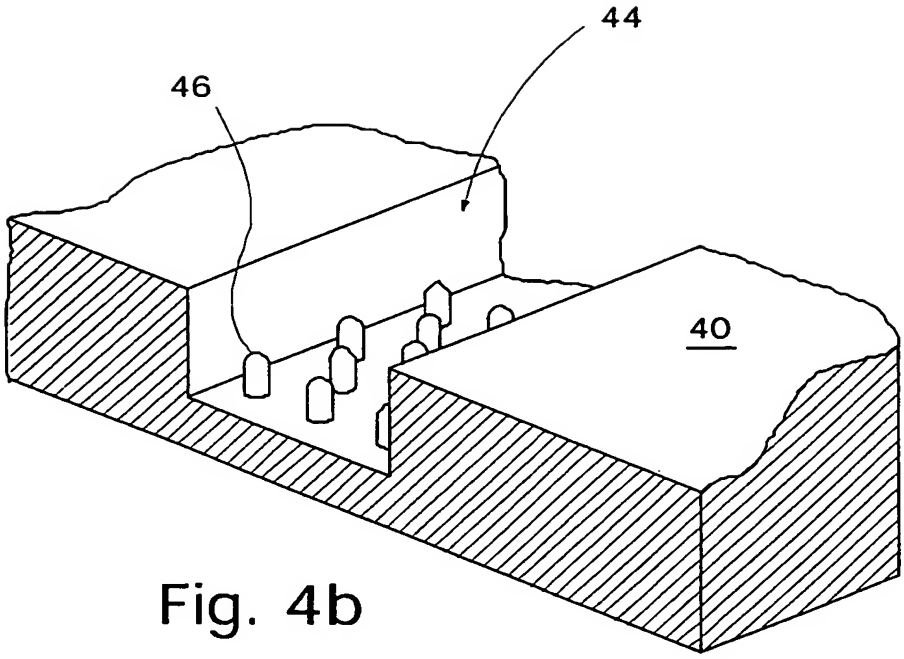


Fig. 4b

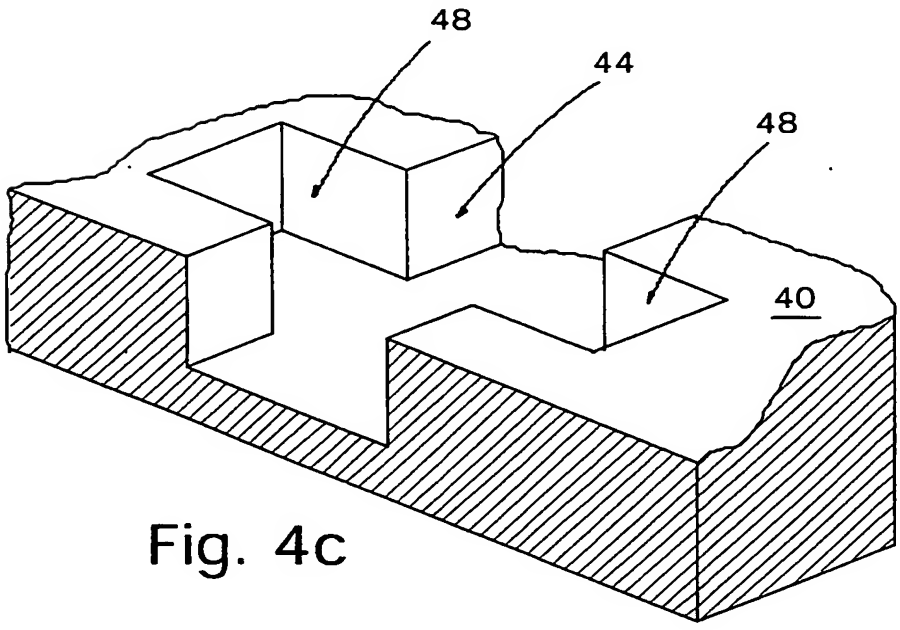


Fig. 4c

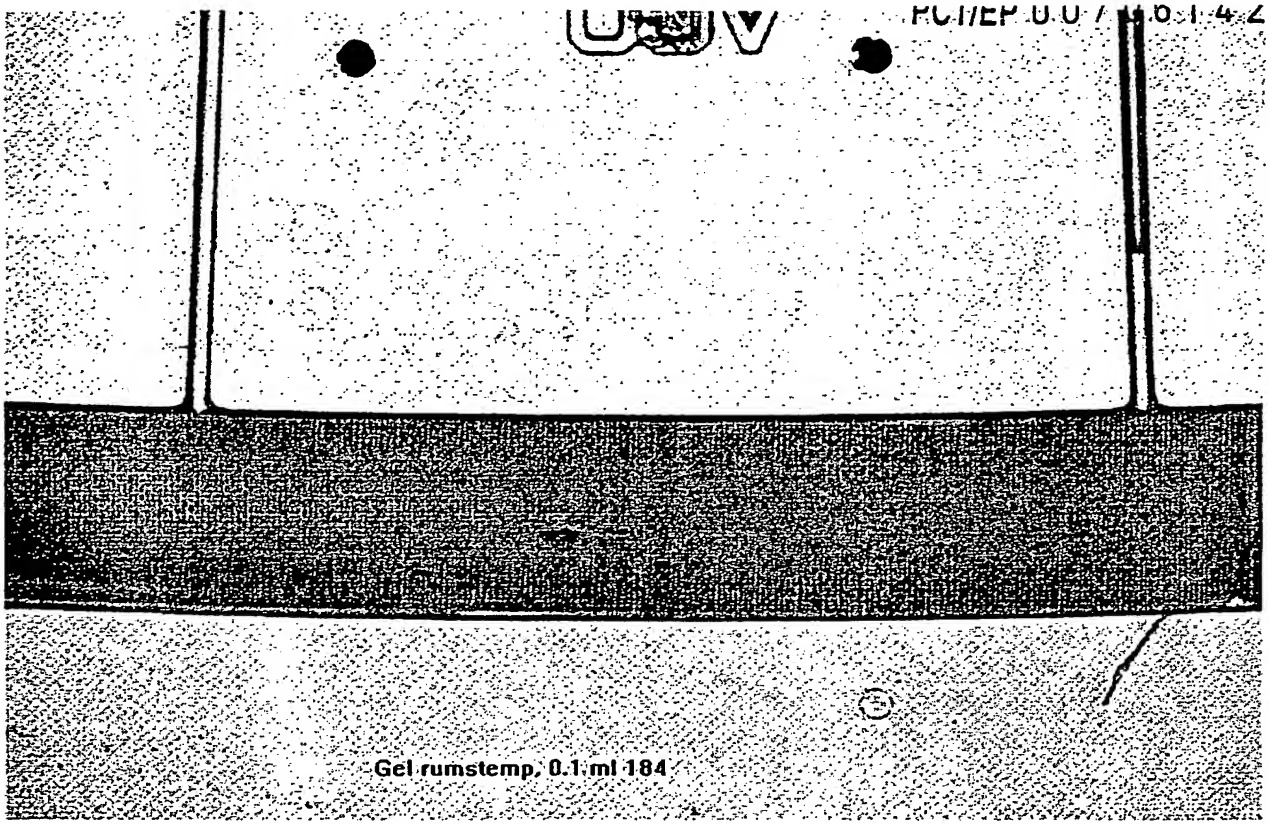


FIG 5A

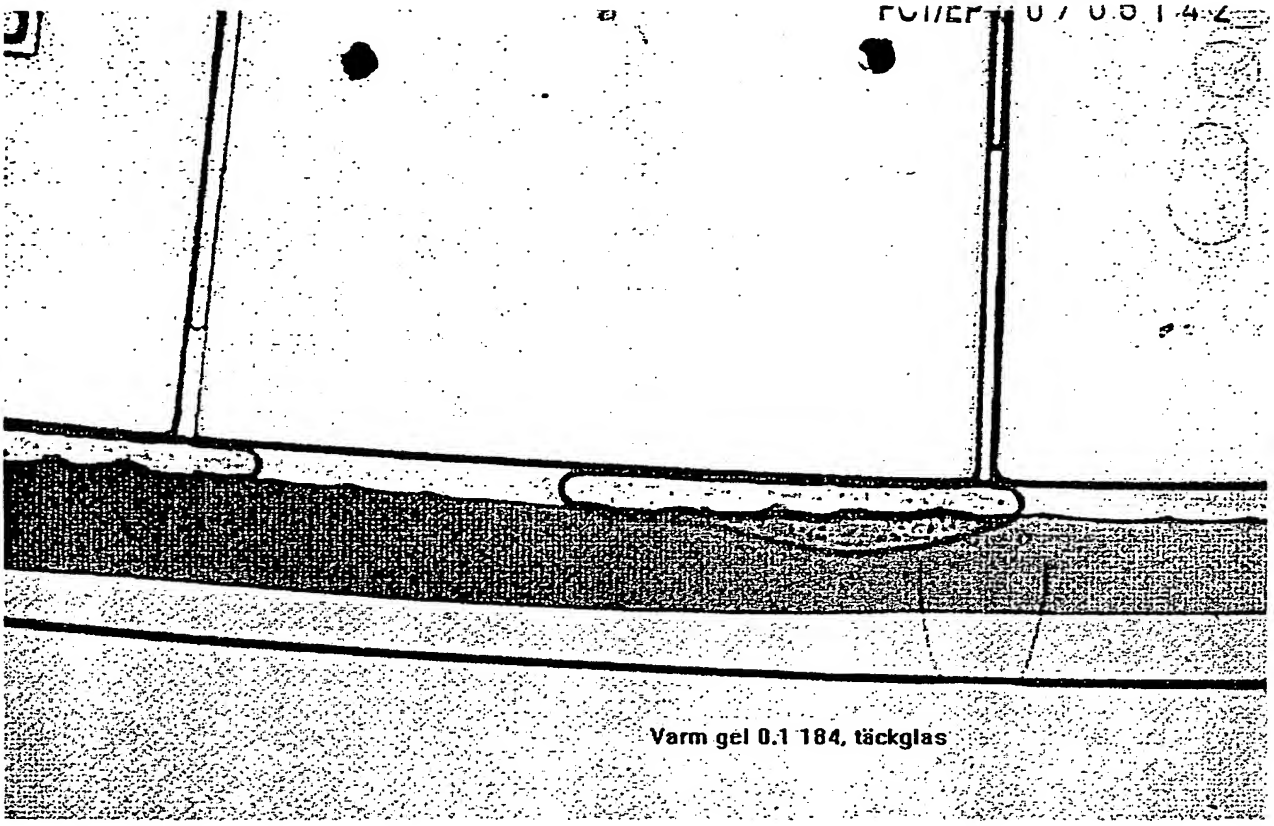


FIG 5B

INTERNATIONAL SEARCH REPORT

Internat' Application No
PCT/EP 00/06142

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 F15C5/00 F16K13/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 F15C F16K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 643 247 A (J.M. FERNANDEZ ET AL.) 1 July 1997 (1997-07-01) column 4, line 66 -column 5, line 9 column 15, line 1 - line 48; figures 15A-15C ---	1
A	ICHIJO H ET AL: "Thermo-responsive gels" RADIATION PHYSICS AND CHEMISTRY,NL,ELSEVIER SCIENCE PUBLISHERS BV., AMSTERDAM, vol. 46, no. 2, 1 August 1995 (1995-08-01), pages 185-190, XP004051389 ISSN: 0969-806X cited in the application the whole document -----	1

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
1 November 2000	08/11/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Goetz, P

1

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internat' Application No
PCT/EP 00/06142

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5643247 A	01-07-1997	AT 168497 T	15-08-1998
		AU 676023 B	27-02-1997
		AU 6231494 A	15-08-1994
		CA 2153990 A	04-08-1994
		DE 69411709 D	20-08-1998
		EP 0680659 A	08-11-1995
		JP 8510597 T	05-11-1996
		WO 9417538 A	04-08-1994

CLAIMS

1. A method of controlling flow of liquids in a micro channel structure comprising a micro channel, said method comprising the steps of:

providing in at least one position, and preferably in a plurality of positions in said micro channel structure a plug of polymer material in each said position, said polymer material having the property of responding to externally applied energy by changing its volume, said polymer material in a first state providing a first volume blocking said channel from liquid flow, and in a second state providing a second volume giving a free path-way for liquid flow; and

selectively applying energy of appropriate type and magnitude to the polymer material of a selected one of said at least one plug so as to cause the volume change between said two states, thereby bringing said polymer to a desired one of said first or second states.

2. The method of claim 1, wherein said polymer material is selected from the group of polymers consisting of heat responsive polymers, light responsive polymers, magnetically responsive polymers, pH responsive polymers and polymers responsive to electric fields.

3. The method of anyone of claims 1-2, comprising that the said polymer material at least partially is anchored to a surface inside said micro channel.

4. The method of anyone of claims 1-3, wherein the polymer material is chemically bonded to the material in said micro channel surface.

5. The method of anyone of claims 1-3, wherein the polymer is anchored in the micro channel by means of a mechanical obstruction in the microchannel.

6. The method of any preceding claim, wherein the material in said micro channel surface comprises a material selected from plastics, e.g. polycarbonates, polystyrenes, cycloolefin polymers; rubbers; metals; carbon; inorganic oxides, nitirides, carbides; silicon; quartz.

7. The method of any preceding claim, wherein the material in said micro channel surface has been subjected to a surface treatment, such as wet etching, plasma treatment, corona treatment, UV treatment, grafting, adsorption coating.

8. The method of any preceding claim, wherein the step of applying energy comprises heating the polymer material and the polymer material comprises a heat responsive polymer.

9. The method of claim 8, wherein said heating is performed by irradiating with electromagnetic radiation, e.g. light, microwaves or infra red radiation, and the polymer material comprises a polymer responsive to electromagnetic radiation, e.g. light, microwaves or infra red radiation).

10. The method of any of claims 1-7, wherein the polymer is light sensitive and the step of applying energy comprises illuminating the polymer material with light of a suitable wave length, and the polymer material comprises a light responsive polymer.

11. The method of any of claims 1-7, wherein the step of applying energy comprises exposing the polymer material to a

magnetic field, and the polymer material comprises a magnetic responsive polymer..

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13. A micro channel valve system, comprising

a plurality of plugs (34) of a polymer material having the property of responding to externally applied energy by changing its volume, said plugs being provided at selected locations within at least one channel (31a-d) of a micro channel structure (20, 22, 24, 26).

14. The valve system according to claim 13, wherein said polymer material is selected from the group of polymers consisting of heat responsive polymers, light responsive polymers, magnetically responsive polymers, polymers responsive to electric fields.

15. The valve system according to anyone of claims 13-14, said polymer material comprising a polymer being selected from the group of polymers consisting of polyvinylethers, polyacrylamides, polyvinylamides, polyalkyleneglycols, celluloseethers, polyacrylates, polymethacrylates; and polymers of N,N-diethylacrylamide, N,N-diethylbisacrylamide, N-vinylcaprolactam, and a polymer obtained by the polymerization of N-isopropylacrylamide and N,N-methylene bisacrylamide.

16. The valve system according to any of claims 13-15, wherein said polymer material is anchored inside said micro channel by chemical bonding.

17. The valve system according to any of claims 13-16, wherein said polymer plug is anchored only over a fraction of the contact surface between the plug in a swelled state and the inner surface of said micro channel (partial anchoring).

18. The valve system according to any of claims 13-16, wherein said polymer plug is retained in a fixed position inside said micro channel by mechanical means.

19. A chemical reactor, comprising a plurality of micro chambers (20) interconnected by micro channels 22, 24, 26), having a valve system according to any of claims 13-18, provided in at least one of said micro channels.

20. The chemical reactor as claimed in claim 19, wherein said chambers and channels are provided in a planar substrate (21).

21. The chemical reactor as claimed in 20, wherein the substrate is of a material selected from the group consisting of plastics e.g. polycarbonates, polystyrenes, cycloolefin polymers; rubbers; metals; carbon; inorganic oxides, nitirides, carbides; silicon; quartz.

22. The chemical reactor as claimed in any of claims 20-21, wherein the substrate is circular.

23. The chemical reactor as claimed in any of claims 20-21, wherein the substrate is rectangular.

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Org. no. 556579-4293

European Patent Office
D-80298 Munich
Germany

Fax +49 89 2399 4465
(17 pages)
Will also be sent by ordinary mail.

Uppsala, May 23, 2001

Re. International patent application PCT/EP00/06142.
Our Ref. No.: GY 0020 PCT (formerly PU 9926-PCT).

This is in response to the written opinion issued February 27, 2001.

Please note our new Ref. No.

Please withdraw the authorization for Anthony J Rollins, Cariona Macleod Hammer and Barry Franks and change the address of correspondence to:

Håkan Bergander
Gyros AB
Uppsala Science Park
SE-751 83 Uppsala
Sweden

Direct telephone number: +46-18-566361. Email: hakan.bergander@gyrosmicro.com.

A new set of claims is attached plus a version in which the amendments have been indicated by underlining and strikethrough.

In the amended independent claims (1 and 13) it has been specified that the polymer material comprises an intelligent polymer. This kind of polymers are well known in the field and have support on page 5, lines 14-26, of the application text as filed.

The amended claims have been drawn up in two-part form as suggested in the Written Opinion. The invention is an improvement relating to valves in micro channels meaning that all features concerning the intelligent polymer should be placed in the characterizing part.

Reference numerals have been inserted into the method claims, where appropriate, as suggested in the Written Opinion.

"pH-responsive polymers" has been added to claim 14. Support is found in the application as filed on on page 5, line 32, and claim 2.

In addition some minor amendments have been made in order to make the claims clearer. These amendments are self-explanatory.

Independent claim 1.
The Written Opinion denies patentablity due to lack of an inventive step over D1 (Ichijo et al., Radiat. Phys. Chem. 46 (2) (1995) 185-190. The reason given is that

(a) D1 discloses a tube in which there is fixed a thermo-responsive polymer that when hot water is poured into the tube shrinks permitting the hot water to pass through. When cold water is poured into the tube the polymer plug swells preventing the cold water to pass through.
(b) D1 in an introductory paragraph refers to the application of stimulus-responsive polymers to micro-machines.

D1 says nothing about response times. Most likely the order hot water – cold water is illustrated in D1 because then hot water easily will reach and penetrate the plug and keep the tube open so that the water can pass though. When starting with cold water and switching to hot water, the valve will be closed at the start and the opening will become dependent on diffusion of heat. In this case the opening will be gradual with a more or less uncontrolled gradual increase in the liquid flow through the valve. This is not desired for most valves for which the objective is a controlled opening that often should be quick.

The uncontrolled opening of the valve of D1 is just one example of the drawbacks of using intelligent polymers (stimulus-responsive) in a macro scale. For macro scale plugs, the response times for swelling/shrinking will in general take unacceptably long time (minutes – hours). There will be a high risk for inhomogeneous absorption of energy and uncontrolled opening/closing etc.

This has later been supported by Liu et al "In-channel processing to create autonomous hydrogel microvalves" in Proceedings of the μTAS 2000 Symposium, Enschede, The Netherlands, 14-18 May, 2000, page 45-48. See in particular "2. Theory" on page 46. Copy enclosed.

It follows that even if D1 suggests incorporating plugs of thermo-responsive polymers as valves, their disadvantages were obvious meaning that the idea was not a common solution to a general problem. People in the field had a resistance to make use of the idea in any kind of valve. This also includes a resistance of using the idea in micro scale valves.

The present inventors recognized and proved that quick and sharp responses could be accomplished in the micro scale. The rational behind this behavior is that in the micro scale plug the energy transport is quick due to short distances. There is nothing about this in D1.

The Written Opinion argues that the general statement about applying a stimulus-responsive polymers to a number of uses, including as an example micro-machines, in combination with the small part of D1 dealing with a valve based on a stimulus-responsive polymer, would hint the person averaged-skilled in the art to use the same kind of valve in a micro-channel. This argument

is unfair. The introductory paragraph of D1 says nothing about the type of function that will utilize the stimulus-response polymer in the micro-machine. D1 does not even say that the micro-machine has a valve.

It follows that that the argument for lack of inventive step is not based on the true facts provided by D1. The argument is based on hindsight. **The rejection of claim 1 based on D1 should be withdrawn.**

Independent claim 13.
Amended claim 13 specifies that the polymer material comprises an intelligent polymer. This kind of polymers is not used in D2 (WO 97 21090, Gamera). This amendment inherently includes that the change of volume is reversible, i.e. the opening/closing can be repeated. Compare the application text page 5, lines 18-20.

The basis for the argument for lack of novelty has been overcome by the amendment. Inventive step in relation to D2 is based on the combination of the facts that (a) the polymer valves of D2 utilize a completely different kind of polymers and are based on polymers that hardly can result in valves that can be repeatedly opened and closed, and (b) D2 gives no hint at using stimulus-responsive polymers in valves.

Dependent claims 2-12, and 14-18.
These claims have novelty and inventive step at least for the same reasons as claims 1 and 13, respectively.

Dependent claims 19-23.
These claims have novelty and inventive step at least for the same reasons as claim 13.

We are looking forward having an International Preliminary Examination Report recognizing patentability for all the claims.

Gyros AB

Håkan Bergander
Patent Manager
G.A. 43194

Encl.

- Amended claims (3x)
- Amended claims with amendments shown (1x)
- Liu et al "In-channel processing to create autonomous hydrogel microvalves" in Proceedings of the μTAS 2000 Symposium, Enschede, The Netherlands, 14-18 May, 2000, page 45-48
- Form for Acknowledgement of Receipt (only sent by ordinary mail)

CLAIMS:

1. A method of controlling flow of liquids in a micro channel structure comprising a micro channel (32), characterized in comprising the steps of:

providing in at least one position, and preferably in a plurality of positions in said micro channel structure a plug of polymer material in each said position, said polymer material (34) comprising an intelligent polymer having the property of responding to externally applied energy by changing its volume, said polymer material in a first state providing a first volume blocking said channel from liquid flow, and in a second state providing a second volume giving a free path-way for liquid flow; and

selectively applying energy of appropriate type and magnitude to the polymer material of a selected one of said at least one plug so as to cause the volume change between said two states, thereby bringing said polymer to a desired one of said first or second states.

2. The method of claim 1, characterized in said intelligent polymer being selected from the group of polymers consisting of heat responsive polymers, light responsive polymers, magnetically responsive polymers, pH responsive polymers and polymers responsive to electric fields.

3. The method of anyone of claims 1-2, characterized in the said polymer material (32) at least partially being anchored to a surface inside said micro channel (34).

4. The method of anyone of claims 1-3, characterized in the polymer material (32) being chemically bonded to the material in said micro channel surface.

5. The method of anyone of claims 1-2, characterized in the polymer material being anchored in the micro channel (34) by means of a mechanical obstruction (42,46) in the microchannel.

6. The method of any preceding claim, characterized in the material in said micro channel surface comprising a material selected from plastics, e.g. polycarbonates, polystyrenes, cycloolefin polymers; rubbers; metals; carbon; inorganic oxides, nitirides, carbides; silicon; quartz.

7. The method of any of claims 3-6, characterized in the material in said micro channel surface having been subjected to a surface treatment, such as wet etching, plasma treatment, corona treatment, UV treatment, grafting, adsorption coating.

8. The method of any preceding claim, characterized in the step of applying energy comprising heating the polymer material and the polymer material comprises a heat responsive polymer.

9. The method of claim 8, characterized in said heating being performed by irradiating with electromagnetic radiation, e.g. light, microwaves or infra red radiation, and the polymer material comprises a polymer responsive to electromagnetic radiation, e.g. light, microvawes or infra red radiation).

10. The method of any of claims 1-7, characterized in the polymer being light sensitive and the step of applying energy comprising illuminating the polymer material with light of a suitable wave length, and the polymer material comprising a light responsive polymer.

11. The method of any of claims 1-7, characterized in the step of applying energy comprising exposing the polymer material

to a magnetic field, and the polymer material comprises a magnetic responsive polymer.

12. The method of any of claims 1-7, characterized in the step of applying energy comprising exposing the polymer material to an electric field, and the polymer material comprises a polymer responsive to electricity.

13. A micro channel valve system, characterized in comprising

a plurality of plugs (34) of a polymer material comprising an intelligent polymer having the property of responding to externally applied energy by changing its volume, said plugs being provided at selected locations within at least one channel (31a-d) of a micro channel structure (20, 22, 24, 26).

14. The valve system according to claim 13, characterized in said said intelligent polymer being selected from the group of polymers consisting of heat responsive polymers, light responsive polymers, magnetically responsive polymers, polymers responsive to electric fields and pH-responsive polymers.

15. The valve system according to any of claims 13-14, characterized in said polymer material comprising an intelligent polymer selected from the group of polymers consisting of polyvinylethers, polyacrylamides, polyvinylamides, polyalkyleneglycols, celluloseethers, polyacrylates, polymethacrylates; and polymers of N,N-diethylacrylamide, N,N-diethylbisacrylamide, N-vinylcaprolactam, and a polymer obtained by the polymerization of N-isopropylacrylamide and N,N-methylene bisacrylamide.

16. The valve system according to any of claims 13-15, characterized in said polymer material being anchored inside said micro channel by chemical bonding.

17. The valve system according to any of claims 13-16, characterized in said polymer plug being anchored only over a fraction of the contact surface between the plug in a swelled state and the inner surface of said micro channel (partial anchoring).

18. The valve system according to any of claims 13-16, characterized in said polymer plug being retained in a fixed position inside said micro channel by mechanical means.

19. A chemical reactor, characterized in comprising a plurality of micro chambers (20) interconnected by micro channels 22, 24, 26), having a valve system according to any of claims 13-18, provided in at least one of said micro channels.

20. The chemical reactor as claimed in claim 19, characterized in said chambers and channels being provided in a planar substrate (21).

21. The chemical reactor as claimed in 20, characterized in the substrate being of a material selected from the group consisting of plastics e.g. polycarbonates, polystyrenes, cyclo-olefin polymers; rubbers; metals; carbon; inorganic oxides, nitrides, carbides; silicon; quartz.

22. The chemical reactor as claimed in any of claims 20-21, characterized in the substrate being circular.

23. The chemical reactor as claimed in any of claims 20-21, characterized in the substrate being rectangular.

CLAIMS:

1. A method of controlling flow of liquids in a micro channel structure comprising a micro channel (32), ~~said method~~characterized in comprising the steps of:

providing in at least one position, and preferably in a plurality of positions in said micro channel structure a plug of polymer material in each said position, said polymer material (34) comprising an intelligent polymer having the property of responding to externally applied energy by changing its volume, said polymer material in a first state providing a first volume blocking said channel from liquid flow, and in a second state providing a second volume giving a free path-way for liquid flow; and

selectively applying energy of appropriate type and magnitude to the polymer material of a selected one of said at least one plug so as to cause the volume change between said two states, thereby bringing said polymer to a desired one of said first or second states.

2. The method of claim 1, ~~wherein~~ characterized in said ~~polymer material~~intelligent polymer being ~~is~~ selected from the group of polymers consisting of heat responsive polymers, light responsive polymers, magnetically responsive polymers, pH responsive polymers and polymers responsive to electric fields.

3. The method of anyone of claims 1-2, characterized in ~~comprising that~~ the said polymer material (32) at least partially ~~is~~ being anchored to a surface inside said micro channel (34).

4. The method of anyone of claims 1-3, characterized in ~~wherein~~ the polymer material (32) ~~is~~ being chemically bonded to the material in said micro channel surface.

5. The method of anyone of claims 1-~~3~~2, ~~wherein~~ characterized in the polymer material being~~is~~ anchored in the micro channel (34) by means of a mechanical obstruction (42,46) in the microchannel.

6. The method of any ~~p~~preceding claim, ~~wherein~~ characterized in the material in said micro channel surface comprising~~es~~ a material selected from plastics, e.g. polycarbonates, polystyrenes, cycloolefin polymers; rubbers; metals; carbon; inorganic oxides, nitirides, carbides; silicon; quartz.

7. The method of any of claims 3-6~~preceding claim~~, ~~wherein~~ characterized in the material in said micro channel surface having~~s~~ been subjected to a surface treatment, such as wet etching, plasma treatment, corona treatment, UV treatment, grafting, adsorption coating.

8. The method of any preceding claim, ~~wherein~~ characterized in the step of applying energy comprising~~es~~ heating the polymer material and the polymer material comprises a heat responsive polymer.

9. The method of claim 8, ~~wherein~~ characterized in said heating being~~is~~ performed by irradiating with electromagnetic radiation, e.g. light, microwaves or infra red radiation, and the polymer material comprises a polymer responsive to electromagnetic radiation, e.g. light, microvawes or infra red radiation).

10. The method of any of claims 1-7, ~~wherein~~ characterized in the polymer ~~is~~ being light sensitive and the step of applying energy comprising~~es~~ illuminating the polymer material with light of a suitable wave length, and the polymer material comprising~~es~~ a light responsive polymer.

11. The method of any of claims 1-7, characterized in~~wherein~~ the step of applying energy comprisinges exposing the polymer material to a magnetic field, and the polymer material comprises a magnetic responsive polymer~~.~~.

12. The method of any of claims 1-7, ~~wherein~~ characterized in the step of applying energy comprisinges exposing the polymer material to an electric field, and the polymer material comprises a polymer ~~resonsive~~responsive to electricity.

13. A micro channel valve system, ~~comprising~~ characterized in comprising

a plurality of plugs (34) of a polymer material comprising an intelligent polymer having the property of responding to externally applied energy by changing its volume, said plugs being provided at selected locations within at least one channel (31a-d) of a micro channel structure (20, 22, 24, 26).

14. The valve system according to claim 13, ~~wherein~~ characterized in said ~~polymer material~~said intelligent polymer beingis selected from the group of polymers consisting of heat responsive polymers, light responsive polymers, magnetically responsive polymers, polymers responsive to electric fields and pH-responsive polymers.

15. The valve system according to any~~one~~ of claims 13-14, characterized in said polymer material comprising an intelligent polymer ~~being~~ selected from the group of polymers consisting of polyvinylethers, polyacrylamides, polyvinylamides, polyalkyleneglycols, celluloseethers, polyacrylates, polymethacrylates; and polymers of N,N-diethylacrylamide, N,N-diethylbisacrylamide, N-vinylcaprolactam, and a polymer obtained by the polymerization of N-isopropylacrylamide and N,N-methylene bisacrylamide.

16. The valve system according to any of claims 13-15, characterized in ~~wherein~~ said polymer material ~~is~~ being anchored inside said micro channel by chemical bonding.

17. The valve system according to any of claims 13-16, ~~wherein~~ characterized in said polymer plug ~~is~~ being anchored only over a fraction of the contact surface between the plug in a swelled state and the inner surface of said micro channel (partial anchoring).

18. The valve system according to any of claims 13-16, ~~wherein~~ characterized in said polymer plug being~~is~~ retained in a fixed position inside said micro channel by mechanical means.

19. A chemical reactor, characterized in comprising a plurality of micro chambers (20) interconnected by micro channels 22, 24, 26), having a valve system according to any of claims 13-18, provided in at least one of said micro channels.

20. The chemical reactor as claimed in claim 19, characterized in ~~wherein~~ said chambers and channels ~~are~~ being provided in a planar substrate (21).

21. The chemical reactor as claimed in 20, ~~wherein~~ characterized in the substrate ~~is~~ being of a material selected from the group consisting of plastics e.g. polycarbonates, polystyrenes, cyclo-olefin polymers; rubbers; metals; carbon; inorganic oxides, nitirides, carbides; silicon; quartz.

22. The chemical reactor as claimed in any of claims 20-21, ~~wherein~~ characterized in the substrate ~~is~~ being circular.

23. The chemical reactor as claimed in any of claims 20-21, ~~wherein~~ characterized in the substrate ~~is~~ being rectangular.

PATENT COOPERATION TREATY

ANKOM

00 20 PCT 2001-06-14

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

BERGANDER, Hakan
GYROS AB
Uppsala Science Park
75183 Uppsala
SUEDE

PCT 11

NOTIFICATION CONCERNING INFORMAL COMMUNICATIONS WITH THE APPLICANT

(PCT Rule 66.6)

	Date of mailing *(day/month/year)* 12.06.2001
Applicant's or agent's file reference PU9926-PCT	**REPLY DUE** within ~~2~~ month(s) from the above date of mailing 01 08 12
International application no. PCT/EP00/06142	International filing date *(day/month/year)* 30/06/2000
Applicant GYROS AB et al.	

An informal communication took place on 05/06/2001, between the International Preliminary Examining Authority and the applicant / the agent.

Invitation pursuant to Rules 66.2 c), 66.3 and 66.4 of the PCT

Further examination of the international application has revealed that the application fails to meet the requirements of the PCT and the Regulations as explained in the attached note (Form PCT/IPEA/428).

The Applicant is hereby **invited**, within the time limit indicated above, **to submit a written reply** accompanied by amendments.

If no reply is submitted, the international preliminary examination report will reflect the opinion expressed by this Authority.

Name and mailing address of the international preliminary examining authority European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Stafl, C Telephone No.+49 89 2399-2698

Form PCT/IPEA/429 (july 1993)

Vertrag über die internationale Zusammenarbeit auf dem Gebiet des Patentwesens
Patent Cooperation Treaty
Traîté de coopération en matière de brevets

PCT

Application No.: PCT/EP00/06142

Note on an informal communication by telephone with the Applicant

Transmittal of a copy of this note with a time limit of **2 month(s)**

Participants

Applicant: GYROS AB

Agent: H. Bergander

Examiner(s): Lemble, Y

Summary of the communication

The new claims were discussed in the light of document D1 and US-A-5 547 472.

In view of the reluctance of the examiner to write a positive IPER, the Applicant asked for a new time limit, in order for him to file modified claims.

05/06/2001
.....
Date *(day / month / year)*

Lemble, Y
.....
Authorized officer of IPEA

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrialapplicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	
Inventive step (IS)	Claims	1-23
Industrial applicability (IA)	Claims	

2. Citations and explanations
   see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

Item V

Independent claim 1.

The document entitled "Thermo-responsive gels", Radiat. Phys. Chem. Vol. 46, No 2, pp. 185-190,1995, by Ichijo et al. (D1) is considered to represent the closest prior art.

Referring to page 5, line 30 to page 6, line 4 of the present application for the interpretation of the last paragraph of independent claim 1, the following features are recognizable in D1 (see figure 11 in combination with the last paragraph of page 190):

a method of controlling flow of liquids in a channel structure, said method comprising the steps of:
providing in at least one position in said channel structure (tube) a plug of polymer material (PVME gel) in said position, said polymer material having the property of responding to externally applied energy by changing its volume, said polymer material in a first state providing a first volume blocking said channel from liquid flow, and in a second state providing a second volume giving a free path-way for liquid flow (see fig.11); and
selectively applying energy of appropriate type and magnitude (hot and cold water) to the polymer material of said plug so as to cause the volume change between said two states, thereby bringing said polymer to a desired one of said first or second states.

The subject-matter of independent claim 1 only differs from this disclosure in that the channel structure is a micro channel structure comprising a micro channel.

In the introductory part of D1 (first paragraph of page 185) is mentioned that one of the field where this type of thermo-responsive gels can be applied is **micro-machines**. With this hint the person skilled in microfabricated channel systems who is seeking a way to provide some means for closing or opening these channels would realise that the working principle of the flow control valve of Fig. 11 of D1 can be readily applied to a micro-channel without any technical difficulty.

Therefore the subject-matter of independent claim 1 does not involve an inventive step, contrary to Articles 33(3) and 33(1) PCT.

Independent claim 13.

The document WO-A-97/21090 (D2) discloses in Figure 11 and page 26, line 25 to page 27, line 10 a micro channel valve system, comprising a plug (cold stamping upper portion of channel) of a polymer material having the property of responding to externally applied energy by changing its volume, said plug being provided at a selected location within one channel of a micro channel structure.

It is obvious to the skilled person that this principle is applicable to a plurality of plugs located at several locations of several micro-channels. It can be noted that claim 13 does not require that the change of volume be **reversible,** or that the plug be a part **separate** from the channel.

Therefore the subject-matter of independent claim 13 does not involve an inventive step, contrary to Articles 33(3) and 33(1) PCT.

Dependent claims 2 to 12 and 14 to 18.

These dependent claims do not appear to contain any additional features which are not known nor obviously derivable from the prior art documents cited above.

Dependent claims 19 to 23.

D2 discloses that the micro channel valve system shown in Figure 11 could be used in a chemical reactor (see page 51 and ff. intituled: "Application and Uses").
Thus, these dependent claims do not appear to contain any additional features which are not known nor obviously derivable from D2.

Item VII

The Applicant may file new claims. To meet the requirements of Rule 6.3 (b) (i) and (ii) PCT, the independent claims should be properly cast in the two part form, with those

features which in combination are part of the prior art (see document D1 or D2) being placed in the preamble.
The second part of the independent claim should contain the features that the invention adds to the prior art. In his letter of reply, the Applicant is invited **to indicate why these features are not obvious to a person skilled in the art.**

Should the applicant file more than one independent claims, attention is drawn to the fact that the application has to comply with the requirements of **unity of invention** (Rule 13 PCT). In his letter of reply, the Applicant is invited **to indicate in which features the common inventive concept is to be seen.**

Reference signs in parentheses should be inserted in the claims to increase their intelligibility (Rule 6.2b PCT).

The description should be adapted to the new claims.

In order to facilitate the examination of the conformity of the amended application with the requirements of Article 34(2)(b) PCT, **the applicant is requested to clearly identify the amendments carried out,** no matter whether they concern amendments by addition, replacement or deletion, and **to indicate the passages of the application as filed on which these amendments are based** (see also Rule 66.8(a) PCT).

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Correspondence with the EPO on PCT Chapter II demands

In order to ensure that your PCT Chapter II demand is dealt with as promptly as possible you are requested to use the enclosed self-adhesive labels with any correspondence relating to the demand sent to the Munich Office.

One of these labels should be affixed to a prominent place in the upper part of the letter or form etc. which you are filing.

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year)	
15 February 2001 (15.02.01)	
International application No. PCT/EP00/06142	**Applicant's or agent's file reference** PU9926-PCT
International filing date (day/month/year) 30 June 2000 (30.06.00)	**Priority date** (day/month/year) 30 June 1999 (30.06.99)
Applicant DERAND, Helene et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

22 January 2001 (22.01.01)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

A. Karkachi

Telephone No.: (41-22) 338.83.38

P. ENT COOPERATION TREAT

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

BERGANDER, Håkan
Gyros AB
Uppsala Science Park
SE-751 83 Uppsala
SUÈDE

Date of mailing (day/month/year)	
19 July 2001 (19.07.01)	
Applicant's or agent's file reference	**IMPORTANT NOTIFICATION**
PU9926-PCT	
International application No.	**International filing date** (day/month/year)
PCT/EP00/06142	30 June 2000 (30.06.00)

1. The following indications appeared on record concerning:

[ ] the applicant [ ] the inventor [X] the agent [ ] the common representative

Name and Address	State of Nationality	State of Residence
ROLLINS, Anthony, John Nycomed Amersham plc Amersham Laboratories White Lion Road Amersham Buckinghamshire HP7 9LL United Kingdom	Telephone No. Facsimile No. Teleprinter No.	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[X] the person [ ] the name [X] the address [ ] the nationality [ ] the residence

Name and Address	State of Nationality	State of Residence
BERGANDER, Håkan Gyros AB Uppsala Science Park SE-751 83 Uppsala Sweden	SE Telephone No. Facsimile No. Teleprinter No.	SE

3. Further observations, if necessary:
Please note that the agent of record has been revoked. Please note the new address for correspondence.

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[X] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[X] other: ROLLINS, A. J.

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer A. Karkachi
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38